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WOOD, PHILLIPS, KATZ, CLARK & MORTIMER
500 W. MADISON STREET
SUITE 3800
CHICAGO, IL 60661

EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,507	HOLM, PER SONNE	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-10,12-22,24-27,30,32-35,39,47,48 and 51-69* is/are pending in the application.

4a) Of the above claim(s) *1,3,5-10,12-22,24-27,39,47,48 and 51-69* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30 and 32-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/28/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment 5/18/09. Claims 1, 3, 5-10, 12-22, 24-27, 30, 32-35, 39, 47, 48 and 51-69 are pending in this application.

Response to the Amendment

Applicants' amendment has overcome the previously stated objections to the specification as well as to the drawings. The claim objections as well as claim rejections under 35 USC 101 and 112, second paragraph have been overcome by applicants' amendments to the claims.

Election/Restrictions

Claims 1-29 and 36-69 have been amended to be compliant with proper claim construction under 35 USC 101 and MPEP § 608.01(n). However, claim 29 is drawn to a cancelled claim and hence, claim will be considered to be dependent from claim 1.

Newly amended claims 1, 3, 5-10, 12-22, 24-27, 39, 47, 48 and 51-69 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Restriction is required under 35 U.S.C. 121 and 372.

This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

In accordance with 37 CFR 1.499, applicant is required, in reply to this action, to elect a single invention to which the claims must be restricted.

Group I, Claims 1, 3, 5-10, 12-22, 24-27, 39, 47, 48 and 51-69, drawn to a method of treating a tumour comprising an adenovirus encoding an E1A that transactivates E1B55kDa in cells and is replication deficient in cells lacking YB-1 in the nucleus.

Group II, Claims 30 and 32-35, drawn to an adenovirus comprising E1A that mediates transactivation of E1B-55K but is replication deficient in cells that lack YB-1.

The inventions listed as Group I-II do not relate to a single general inventive concept because they lack the same or corresponding technical feature. The "special technical feature" of is an adenovirus that transactivates early genes but does not induce YB-1 and within an adenovirus is selectively replicative in YB-1 cells, which is shown by :LaFace et al below, to novelty of inventive step and does not make a contribution over the prior art.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 1, 3, 5-10, 12-22, 24-27, 39, 47, 48 and 51-69 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. Claims 30 and 32-35 are under examination.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent

Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, the letter stating that the contents of the sequence listing and the CRF are the same does not also state that the submission does not constitute new matter. Such a letter is required.

Claim Objections

Claims 32 and 34 are objected to because of the following informalities: the claims are drawn to an E1A protein that comprises one or several mutations and deletions where the deletion is within a CR3 region, a N-terminus region, a C-terminus region, or combination thereof. The antecedent basis for "the deletion" is inferred, however, should be recited as --wherein at least one of the deletions is--. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30 and 32-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the office action mailed 10/28/08 and restated below.**

The instant claims are drawn to an isolated adenovirus that is replication deficient in cells that lack YB-1 in the nucleus and is replication competent in cells have YB-1 in the nucleus.

The adenovirus comprises an E1A viral oncogene protein that mediates transactivation of E1B-55K and does not induce YB-1 activity in a nucleus of a cell in which the oncogene is present. The base claims thus provides no structural requirements of the E1A protein, only functionally requirements. Claim 32 limits the E1A protein to one comprising "one or several mutations or deletions whereby the deletion is within "the CR3 region", "the N-terminus" and "the C-terminus" wherein in claim 33 RB is bound by E1AA. Claim 34 limits the E1A protein to one comprising "one or several mutations or deletions whereby the deletion is within the CR1 and/or CR2 region of the E1A protein wherein in claim 35 E1A is incapable of binding Rb. Hence, the claims are directed a large genus of adenovirus due to the large number of E1A proteins that are encompassed by the claims. Specifically, the E1A protein can be any so long as there is a deletion within the Cr1, Cr2, Cr3, N-terminus or C-terminus. Functionally, the protein must transactivate E1B-55K but not induce YB-1 in a nucleus and in some cases not bind to Rb. The claims due to the large breadth of claims and the lack of structural-functional correlation lack written description of the genus of E1A proteins. The written description requirement under 35 USC 112, first paragraph may be met by sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. Applicant is referred to the Guidelines on Written Description published at FR 66(4) 1099-1111 (January 5, 2001) (also available at www.uspto.gov).

Applicants characterize the effect of mutations in E1A with the goal of a designing a protein that activates E1B but does not activate YB-1. As well, mutants that bind RB or cannot are claimed. The specification teaches,

> In order to confer the capability to not bind to Rb, the following deletions of the E1A oncoprotein are, for example, possible: Deletion in the CR1 region (amino acid positions 30-85 in Ad5) and deletion of the CR2 region (amino acid positions 120-139 in AD5). In doing so, the CR3 region is maintained and can have its transactivating function on the other early viral genes.
>
> In contrast thereto, the following deletions to the E1A oncoprotein are in principle possible in order to impart E1A the capability to bind to Rb: deletion of the CR3 region (amino acid positions 140-185); deletion of the N-terminus (amino acid positions 1-29); deletion of amino acid positions 85-119; and deletion of the C-terminus (amino acid positions 186-289). The regions recited herein do not interfere with the binding of E2F to Rb. The transactivating function remains, however, is reduced compared to wild type Ad5.

As regards the mutations in E1A, The specification does not provide any information on what amino acid residues in particular are necessary and sufficient for the combined function of lack of transactivation of YB-1, transactivation of E1B55k and loss of or maintenance of Rb binding. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in E1A polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. It is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. Furthermore, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the

relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see below). As regards deletions in the CR3 region, N-terminus, C-terminus, CR1 and/or Cr2, applicants only disclose one deletion in the CR1 region (amino acid positions 30-85) and one in the CR2 region (120-139 of Ad5) that lead to loss of RB binding. Deletions that do not affect Rb binding the specification teaches one deletion in the CR3 region of amino acids 140-185 one in the N-terminus 1-29 a deletion in 85-119 and one deletion in the C-terminus 186-129. All of these mutations are in the E1A region of Ad5.

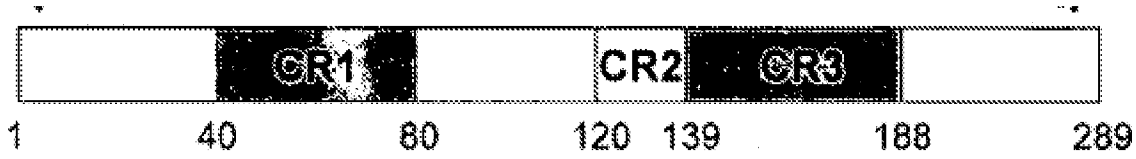
The scope of these deletions is not commensurate in scope with the broad genus of any oncogene that transactivates E1b-55K but does not activate YB-1 further comprising one or several mutations or deletions.

An adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of claimed nucleic acid sequences. A particular protein sequence determines the protein's structural, and functional properties, and the ability to determine a priori whether a homologue or variant can function in the recited invention is not a high art. A knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e., expectedly intolerant to modification), and detailed knowledge of the ways in which a protein's structure relates to its functional usefulness is required (see Guo et al and Lesk et al). By claiming all viral oncogenes with the functional properties described in terms of transactivation ability and binding without

defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See Fiers 7. Reveb 25 USPQZd 1601 (CA FC 1993) and Regents of the Univ. Calif v. Eli Lilly & Co. 43 USPQZd 1398 (CA FC, 1997)). In this case, applicants have only disclosed Ad5 E1A deletions in which the resulting protein can mediate E1B transactivation but not YB-1 and can or cannot bind Rb. Given the large size and diversity of fragments generated by mutation or deletion CR1, CR2, CR3 or at the N and/or C-terminus and the inability to determine which will also have the essential element, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of no species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Response to Amendments

Applicants response filed 4/28/09 has been reviewed but is not persuasive. Claim 30 is drawn to an adenovirus comprising an E1A protein with the following functional properties; it transactivates E1B-55K and does not induce YB-1 activity and is part of an adenovirus that replicates in YB-1 cells but not in cells lacking YB-1. Adenovirus 5 E1A is detailed below:



Claim 30 does not recite any structural properties but embraces naturally occurring E1A proteins as well as modified proteins wherein the modification is non-limiting. Claim 32 recites that the E1A protein comprises one or several mutations and deletions where the deletion is within a CR3 region, a N-terminus region, a C-terminus region, or combination thereof. This is an enormous

number of modifications as these regions cover a great portion of the protein. Secondly, a deletion within the recited region can be 2 nucleotides, 3 nucleotide. Thirdly, it does not indicate what the other deletions or mutations are. Claim 34 recites, that E1A comprises one or several mutations or deletions, whereby the deletion is preferably a deletion in the CR1 region and/or the CR2 region. Again this is also an enormous number of different modifications. Claims 33 and 35 further require that the protein bind or not bind respectively Rb. Applicants argue that these embodiments are disclosed in the specification and once coupled with the knowledge available in the art provide adequate written description of the claimed genus of E1A proteins. However, the genus as recited in the claims is larger than the disclosure supports. Specifically, the claims recite any E1A, from any subtype, genotype or source that has certain functional properties wherein the structural properties as set forth above are quite broadly recited.

As set forth in the rejection above, the specification lacks any guidance as to the structural requirements of the E1A protein to mediate the recited functions and therefore, the specification has failed to describe the genus such that the nexus of structure and function is apparent. Given the lack of disclosure as to the structural requirements of the of the diverse group of recited genus, the skilled artisan cannot envision the detailed structure of the broad class of E1A proteins regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that the sequence is part of the invention and a reference to a potential method for isolating it.

The specification teaches 1) intact CR3 mediates transactivation regardless of YB-1 cell status "The transactivating function is primarily based on the presence of the CR3 region in the E1A protein. The amino acid sequence of CR3 is unaltered in the aforementioned adenoviruses.

This results in a transactivation of the early genes E1B, E2, E3 and E4 independent from the presence of YB-1 in the nucleus or in the cytoplasma." 2) A CR3 deleted virus, dl520, meets the limitations of the instant claims in that it encodes an E1A protein that mediates transactivation but the virus is replication deficient in YB-1 minus cells but replicates in YB-1 + cells. In this case, the entire CR3 region is deleted. "In the recombinant adenovirus dl520, however, the CR3 region has been deleted. Thus dl520 expresses a so-called E1A12S protein which does not comprise the amino acid sequence of the CR3 region. As a consequence, dl520 can exert a very weak transactivating function only, in particular on the E2 region, and thus does not replicate in YB-1 nucleus-negative cells. In YB-1 nucleus-positive cells YB-1 is transactivating the E2 region and thus allows an efficient replication of d 1520." 3) Deletion of BOTH CR1 and CR2 result in a virus that replicates in YB-1 + cells. "Insofar this example is another proof that a modified E1A oncogene protein which, as depicted in FIG. 7, comprises, for example, only the CR3 region and which is lacking the CR1 region and CR2 region, provides for the required transactivation in YB-1 nucleus-positive cells which is required for the replication of adenoviruses in accordance with the present invention, which results in viral replication." 4) Rb binding is mediated by E1A and virus that can bind Rb are characterized in the art, " In a preferred embodiment of the two uses according to the invention, the virus, in particular the adenovirus, is selected from the group comprising Ad.DELTA.24, dl922-947, E1Ad/01/07, dl1119/1131, CB 016, dl520 and viruses which are lacking an expressed viral E1A oncogene which is capable of binding a functional Rb tumor suppressor gene product." And those that cannot "the deletion is preferably in the CR1 region and/or the CR2 region of the E1A oncogene protein. In connection therewith it is intended that the viral oncogene protein is not able to bind

to Rb." Hence, the specification describes two species of proteins. The first binds Rb, transactivates early proteins and does not induce YB-1 activity and comprises art known E1A proteins with CR3 deletions. The second does not bind Rb, transactivates early proteins and does not induce YB-1 activity and comprises CR3 but lacks CR1 and CR2. Neither of the species allow a person to identify E1a proteins with several mutations or deletions nor deletions within regions. Simply put the two species encompass a narrow genus.

Regarding what is taught in the art, applicants argue that E1A mutants are known that retain transactivation ability. Specifically, applicants argue that the art has demonstrated what domains are capable of mediating transactivation. However, the claims recite two distinct genus of proteins 1) an E1A protein that transactivates E1B55K, that does not activate YB-1 and that binds to Rb and 2) an E1A protein that transactivates E1B55K, that does not activate YB-1 and that does not bind to Rb. Hence, there are requirements above and beyond the region required for transactivation, the protein must also not induce YB-1 and must either bind or not bind to Rb. As well, if the E1A protein must only mediate transactivation, there are numerous proteins disclosed in the prior art of which applicants have apprised the practitioner and which would anticipate the instant claims. Furthermore, it is not clear that any regions defined for Ad5 (as in the instant specification) would correlate to those from other adenovirus. Jelmsa et al teaches that the adenovirus serotypes differ in part in the structures of E1A, "The domain defined here corresponds closely to conserved region 3, a sequence of residues that is highly conserved between Ad5, Ad7, Ad12, and SA7 (Kimelan et al., 1985; Moran and Mathews, 1987; Schneideretal., 1987). However, there are some interesting differences between the predicted E1A proteins of these viruses. It is only in Ad5 that the N-terminal end of the conserved

sequence corresponds to the beginning of the unique 13 S region. In Ad7 and Adl2, some 13 residues of the conserved region lie before the 12 S 5' splice site and so are common to both 12 and 13 S products. In SA7, on the other hand, the unique 13 S region is enlarged by about 29 nonconserved residues, which precede the conserved region. From the present results on Ad5, it seems likely that in these other viruses, the domain for transactivation corresponds to the conserved region alone, but it would be interesting to know how close this correspondence is (page 500)"

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 30, 32-35 stand rejected under 35 U.S.C. 102(b) as being rejected by LaFace et al (US 6,649,158; see entire document). **This rejection is maintained for reasons of record in the office action mailed 10/28/08 and restated below.**

LaFace teaches mutations in E1a that will and will not affect Rb binding. "In the preferred practice of the invention, the Rb binding deletions are represented by elimination of amino acids from about 111-127, preferably from about 111-123. More preferred is a vector wherein said deletion in the E1a-p300 binding domain comprises a deletion of the codons for amino acids 4 to 25 of the adenoviral E1a gene product. More preferred is a vector wherein deletion in the E1a-Rb binding domain comprises a deletion of the codons for amino acids 111-

123 of the adenoviral E1a gene product". Absent evidence to the contrary such an oncogene will given the similarity to the instant deletions mediate transactivation of E1B-55K and not for YB-1 binding.

Response to Amendments

Applicants response filed 4/28/09 has been reviewed but is not persuasive. Applicants' argue that LaFace fails to appreciate isolating adenoviruses that are unable to replicate in a cell where YB-1 is not present in the nucleus, but can replicate in a cell where YB-1 is present in a nucleus and possesses particular E1A mutant proteins that support replication of the adenovirus via transactivation. However, as stated the mutations, absent evidence to the contrary, the virus of LaFace et al inherently comprises this property. There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003) (rejecting the contention that inherent anticipation requires recognition by a person of ordinary skill in the art before the critical date and allowing expert testimony with respect to post-critical date clinical trials to show inherency); see also Toro Co. v. Deere & Co., 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); Abbott Labs v. Geneva Pharms., Inc., 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1310 (Fed.Cir.1999) ("If a product that is offered for sale inherently possesses each of the limitations of the claims, then the

invention is on sale, whether or not the parties to the transaction recognize that the product possesses the claimed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Maria B Marvich, PhD
Primary Examiner
Art Unit 1633

/Maria B Marvich/
Primary Examiner, Art Unit 1633